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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/699,679	10/30/2000	Evan C. Unger	UNGR-1598	8248

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EXAMINER	
COTTON, ABIGAIL MANDA	

ART UNIT	PAPER NUMBER
1617	

DATE MAILED: 07/28/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/699,679	UNGER ET AL.	
	Examiner	Art Unit	
	Abigail M. Cotton	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 May 2006 and 08 February 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *3,4,6-17,22-35,61 and 63-81* is/are pending in the application.

4a) Of the above claim(s) *12 and 13* is/are withdrawn from consideration.

5)☒ Claim(s) *66-81* is/are allowed.

6)☒ Claim(s) *3-4, 6-11, 14-17, 22-35, 61 and 63-65* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on February 8, 2006, has been entered.

Claims 3-4, 6-17, 22-35, 61 and 63-81 are pending in the application, with claims 12-13 having been withdrawn as drawn to a non-elected invention. Accordingly, claims 3-4, 6-11, 14-17, 22-35, 61 and 63-81 are being examined on the merits herein.

In Paper No. 22B filed on April 10, 2003, Applicant made an election of the claims categorized in Group XII and the species wherein R1 is acyl of 18 carbons, R2 is H, R3 is alkylene, R4 is acyl of 18 carbons, P is PEG-3400 and T is a peptide having sequence CRGDC, and wherein the two cysteines are linked together via a disulfide linkage. Claims 3-4, 6-11, 14-17, 22-35, 61 and 63-65 as well as newly added claims 68-81 are directed to the elected species.

The elected species was found to be free of the art, as set forth in the Office Action mailed on November 9, 2005, and thus the claims are also free of the art to the

extent they read on the elected species. In particular, claims 66-67 and newly added claims 68-81, which are directed only to the elected species, are found to be allowable.

The search has been extended to include a subgenus of claim 17 wherein R1 and R4 are acyl groups of 19-23 carbon atoms, R2 is a lower alkyl, R3 is an alkylene, P is a PEG hydrophilic polymer and T is a targeting ligand directed to GPIIbIIa receptor such as RGD.

Applicant's arguments filed February 8, 2006 have been fully considered but they are not persuasive. The claims remain rejected as set forth below.

Claim Rejections - 35 USC § 103

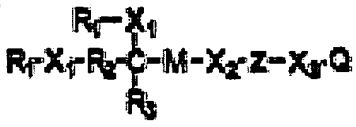
The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 3-4, 6-11, 14-17, 22-35, 61 and 63-65 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 96/40285 to Unger et al, published December 19, 1996.

Unger et al. teaches novel targeted compositions which may be used for diagnostic and therapeutic use, such as for therapeutic ultrasond (see abstract, in particular.) Unger et al. teaches that the composition can comprise a vesicle composition having an aqueous carrier, vesicles comprising a lipid and a gas, such as gas filled liposomes (see page 4, lines 20-30, page 9, lines 15-25 and page 12, lines 25-33, in particular), and thus teaches a targeted vesicle composition for therapeutic or diagnostic use *in vivo* having an aqueous carrier and gas filled liposomes, as recited in claim 17. Unger et al. further teaches that exemplary lipids that can be used to prepare the liposomes can comprise phosphatidyl cholines such as dioleylphosphatidylcholine, dimyristoylphosphatidylcholine, and others (see page 23, lines 15-34, in particular), and thus teaches the gas filled liposomes comprising the phosphatidylcholine as recited in claim 17.

Unger et al. further teaches that the composition can comprise a compound having the formula:



Where Q is a targeting ligand (see page 61, line 1 through page 62, line 33 and claim 136, in particular.) It is noted that the compound as recited in claim 136 of Unger

et al. meets the limitation of the instant structure in that the carbon atom of the structure is linked to R^2-X^1-R^1 at one end, and X^1-R^1 at the other, and R^3 at the 3rd position. Unger et al. defines R^2 as being an alkylene moiety of from 1-30 carbon atoms, which encompasses the instantly claimed species of R^3 as ethylene. Regarding the moieties R^1-X^1 as recited in instant claim 17, Unger et al. teaches that X^1 can be -C(=X^5)-X^4, where X^5 can be O, X^4 can be –NR^4- and R^4 can be an alkyl of 1-10 carbon atoms, as in the instantly claimed species of R^2 as a lower alkyl, and thus teaches the moiety –C(=O)-N(alkyl)- that meets the limitation of the fragment C(=O)-N(R^2)-, as recited in claim 17. Regarding the acyl moiety R^1, Unger teaches that the alkyl group connected to –C(=O)-N(alkyl) (and that thus forms an acyl group) can comprise an alkyl of 1 to 50 carbons, and thus teaches an acyl group that encompasses the claimed species of R^1 that has from 19 to 23 carbon atoms. Regarding R^3, Unger et al. teaches that the moiety can be hydrogen or an alkyl of 1 to 10 carbons, and thus teaches the claimed species of R3 that is an alkylene, as recited in claim 17.

Unger et al. teaches a bond between the central carbon C and the moiety M, and thus teaches R^6 is a direct bond, as recited in claim 17. Regarding the moiety X^1 as recited in claim 17, Unger et al. teaches that the moiety M can comprise –R^5-C(=X^5)-X^4, where R^5 can be a direct bond, X5 can be O, and X4 can be NR4, with R4 being hydrogen or an alkyl of 1 to 10 carbon atoms. Thus, Unger et al. teaches that M can be the moiety –C(=O)-N-alkyl-, which meets the limitation of X^1, as recited in claim 17. Regarding the moiety P as recited in claim 17, Unger et al. teaches that X^2 connecting

to M can be a direct bond, and a moiety Z can be a hydrophilic polymer, such as polyethylene glycol (see also claim 146, in particular), which meets the limitation of the claimed species of P that is a PEG hydrophilic polymer.

Regarding the moieties R^7 and X^2, as recited in claim 17, Unger et al. teaches that a direct bond between the hydrophilic polymer and a moiety X^3 can be formed, and furthermore teaches that X^3 can comprise groups such as $-R^5-C(=X^5)-X^4$, where R^5 can be a direct bond, X^5 can be oxygen and X^4 can be NR^4, with R^4 being hydrogen or lower alkyl of 1 to 10 carbon atoms, and thus teaches the moiety –C(=O)-N-alkyl, which meets the limitation of X2 as recited in claim 17. Regarding the moiety T as recited in claim 17, Unger et al. teaches that the compound can have a targeting ligand Q, and further teaches that such targeting ligand may target the glycoprotein GPIIbIIa receptor (see also claim 151, in particular), and thus teaches the claimed species of targeting ligand.

Unger et al. does not teach a specific embodiment of the compound having a combination of the targeting ligand that targets the GPIIbIIa receptor and the hydrophilic polymer that is a polyethylene glycol, as in the elected species of compound.

However, it is considered that one of ordinary skill in the art at the time the invention was made would have found it obvious to provide the compound that meets the limitation of the formula (IV) as claimed and in particular the elected species of such formula, along with a targeting ligand that targets the GPIIbIIa receptor and the

hydrophilic polymer that is a polyethylene glycol, because Unger et al. teaches the compound having the structure that overlaps with and/or meets the limitations of the claimed species, and furthermore teaches that the compound can comprise targeting ligands that include the GPIIbIIa receptor as claimed and the polyethylene glycol hydrophilic polymer as claimed, and teaches such compound is useful in a vesicle composition for diagnostic and therapeutic use. Accordingly, it is considered that one of ordinary skill in the art would have been motivated to provide the claimed compound with the elected species of targeting ligand and hydrophilic polymer, with the expectation of providing a suitable compound for formulation in a vesicle composition for diagnostic use. Accordingly, claim 17 is obvious over the teachings of Unger et al.

Regarding claims 3-4, 61 and 63, Unger et al. teaches the compositions of the claims insofar as they read on the elected species, as discussed above. Regarding claims 6-9, Unger et al. teaches the hydrophilic polymer can be polyethylene glycol (see claim 147, in particular.) Regarding claim 10, Unger et al. teaches that a molecular weight of the hydrophilic polymer such as polyethylene glycol may be in the range of from 100 to 10,000 and all combinations and subcombinations of ranges therein (see page 62, lines 20-33, in particular.) Accordingly, it is considered that one of ordinary skill in the art at the time the invention was made would have found it obvious to vary and/or optimize the molecular weights of the polyethylene glycol provided in the composition, such as to provide PEG-3400, according to the guidance provided by Unger et al, to provide a composition having desired properties. It is noted that

"[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955.)

Regarding claims 11 and 14, Unger et al. teaches that cyclic peptides comprising linked cysteine groups (sulfur containing amino acids) can be formed with targeting groups such as RGD (see page 58, lines 1-30, in particular), and thus teaches the targeting ligand of the claim. Regarding claims 15-16, Unger et al. teaches suitable targeting ligands that meet the limitations of the claim, and that can be cyclic and have groups Saa that are cysteine or penicillamine (see page 55, line 1 through page 59, line 10, in particular), as recited in the claims.

Regarding claim 22, Unger et al. teaches that the phosphatidylcholine provided in the composition can be dipalmitoylphosphatidylcholine (see page 23, lines 15-34, in particular.) Regarding claims 23-24, Unger et al. teaches that the lipids can comprise phosphatidylethanolamines such as dipalmitoylphosphatidylethanolamine (see page 23, lines 15-33, in particular.) Regarding claim 25, Unger et al. teaches that the lipids can comprise dipalmitoylphosphatidic acid (see page 23, lines 15-34, in particular.)

Regarding claims 26-29, Unger et al. teaches that the vesicles can comprise a gas such as a perfluorocarbon, including perfluoromethane, perfluoropropane and perfluorobutane, among others (see page 32, lines 3-18, in particular), and thus teaches

the gases as recited in the claims. Regarding claims 30-33, Unger et al. teaches the gas can b derived from a gaseous precursor such as perfluoropentane that is converted to a gas at 37°C (see page 33, lines 16-33, in particular), and thus teaches the gaseous precursors of the claims. Regarding claims 34-35, Unger et al. also teaches that the composition can comprise bioactive agents such as urokinase, heparin, and others (see page 83, lines 9-24, in particular.)

Regarding claims 64-65, Unger et al. teaches that the targeting ligand can comprise a peptide having numbers of amino acids that meets the limitations of the claims, and that can be cyclized as claimed (see page 55, line 1 though page 59, line 20, in particular.)

Accordingly, claims 3-4, 6-11, 14-17, 22-35, 61 and 63-65 are obvious over the teachings of Unger et al.

Response to Arguments

Applicant's arguments filed February 8, 2006 have been fully considered but they are not persuasive.

In particular, Applicants argue that the disclosure is not specific enough to provide motivation to modify the teachings of Unger et al. to incoporate the claimed

targeting ligand T (e.g. RGD) and hydrophilic polymer (e.g. PEG.) Applicants assert that the very large number of compounds taught by Unger et al. requires more than merely a generic mention of a class of compounds in order for one of ordinary skill in the art to be motivated to modify the compounds of Unger et al. to arrive at the claimed invention. Applicants point out that the majority of compounds that are specifically exemplified by Unger et al, as in Examples 1, 14 and 47, do not having diamide groups as claimed.

The Examiner respectfully disagrees. Unger et al. teaches and claims embodiment of a compound that meets the structural limitations of the diamide of the claim (see claim 136, in particular), as discussed above, and that contains a targeting ligand (Q) and hydrophilic polymer (Z.) Regarding the hydrophilic polymer, Unger et al. teaches and claims that the hydrophilic polymer Z as provided in the structure of claim 136, can comprise polyethylene glycol (see claim 147 depending from claim 136, in particular.) Regarding the targeting ligand, Unger et al. teaches and claims that the targeting ligand Q as provided in the structure of claim 136 can comprise a targeting ligand that targets a cell or receptor selected from a group of only 5 cells or receptors, and including the glycoprotein GPIIbIIa receptor that is the elected species of targeting ligand (see claim 151 depending from claim 136, in particular.) Accordingly, it is considered that one of ordinary skill in the art would have had sufficient motivation, based on the teachings of Unger et al, to select the diamide compound having the polyethylene glycol hydrophilic polymer and targeting ligand corresponding to the

elected species, with the expectation of providing a suitable compound for diagnostic and therapeutic processes, as taught by Unger et al.

Allowable Subject Matter

Claims 66-81 are allowed.

Claims 66-81 are allowed because the composition having the specific compound as recited in claim 66, from which claims 67-81 depend, is not taught or suggested by the closest prior art of record. The closest prior art of record is WO 96/40285 to Unger et al, which teaches diagnostic and/or therapeutic compositions having a compound with a hydrophilic polymer Z and targeting ligand Q, as shown for example in claim 136 or the Unger et al. reference. However, the specific compound as recited in instant claim 66 does not fall within the scope of the class of compounds encompassed by the compound formula taught by Unger et al. In particular, the general compound formula taught by Unger et al. does not encompass compounds having R^7 as an ethylene group and X2 as $C(=X^3)$, with P as PEG-3400 and T as the peptide CRGDC, as required by claim 66. Accordingly, claim 66 and the claims depending therefrom are allowable over the prior art.

Conclusion

Claims 66-81 are allowed, and claims 3-4, 6-11, 14-17, 22-35, 61 and 63-65 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Abigail M. Cotton whose telephone number is (571) 272-8779. The examiner can normally be reached on 9:30-6:00, M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

AMC

SREENI PADMANABHAN
SUPERVISORY PATENT EXAMINER